REMARKS

Applicant and his counsel wish to thank the Examiner for discussing the Office Action (mailed September 15, 2004) and merits of the application with the undersigned at a telephonic interview on November 9, 2004.

Claims 1-12 and 16-27 are pending in the present application. Applicant notes with appreciation that the Examiner has withdrawn previous rejections. In particular, in the Office Action mailed September 15, 2004, the Applicant notes that the Examiner has removed the prior new matter rejection under 35 U.S.C. §112, first paragraph (Office Action, page 2). In addition, the Examiner has indicated that the following rejections have been removed:

a) Claims 1-12 and 16-27 under 35 U.S.C. §112, first paragraph (new matter and enablement), pages 2-7, paragraph 5;

b) Claims 1-12 under 35 U.S.C. §112, second paragraph;

c) 1, 3-5, and 7-12 under 35 U.S.C. §102(b), pages 8-9;

d) 1, 3-5, and 7-12 under 35 U.S.C. 102(b), pages 9-10;

e) Claims 1-12 under 35 U.S.C. §112, second paragraph, page 9, paragraph 9;

f) Claims 16-27 under 35 U.S.C. §112, second paragraph, page 9, paragraph 10;

g) Claims 16-27 under 35 U.S.C. §112, second paragraph.

With respect to the rejection listed as a), above, Applicant notes that, in addition to the enablement rejection set forth in paragraph 5, the original 112, first paragraph rejections on pages 2-7 included the new matter rejection set forth in paragraph 4 (pages 2-3) of the Office Action mailed March 19, 2004. Applicant respectfully requests clarification that the new matter rejection of paragraph 4 has also been withdrawn.

With respect to the rejection listed as d), above, Applicant notes that the original 102(b) rejection was applied to claims 1, 3-5, 7, 9, 11, 16, 18, 19, 24 and 26, and it appeared on pages 9 and 10, paragraph 8 of the Office Action mailed March 19, 2004. Although the Examiner indicates that this rejection has been withdrawn with respect to Claims 1, 3-5 and 7-12, the absence of any further discussion of this rejection suggests that the Examiner did not intend to sustain the rejection against Claims 16, 18, 19, 24 and 26. The following response is drafted in the belief that this rejection under 35 U.S.C. 102(b) of Claims 16, 18, 19, 24 and 26 had also been withdrawn. If this is not correct, Applicant requests clarification as to the status of these claims.

With respect to the rejections listed as e) and f), above, Applicant notes that paragraphs 9 and 10 of the Office Action mailed March 19, 2004 are on page 10 rather than page 9. Clarification is respectfully requested.

In the Office Action mailed September 15, 2004, the Examiner has made new objections and rejections. For clarity, the objections and rejections at issue are set forth by number in the order they are addressed herein:

1. Claim 6 is objected to as being dependent on a rejected base claim (Office Action item 5, page 3);
2. Claims 1-12 are rejected under 35 U.S.C. §112, second paragraph, for alleged lack of clarity (Office Action item 6, page 3);
3. Claims 1, 3-5 and 7-12 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Mahan, *et al* (U.S. Patent No, 5,434,055, hereinafter "Mahan")(Office Action item 7, page 4);
4. Claims 1, 3-5, 7-12 and 16-27 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Curtiss, III, *et al* (U.S. Patent No, 6,780,405, hereinafter "Curtiss")(Office Action item 8, page 5);
5. Claims 1, 3-5, and 7-12 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Mekalanos, *et al* (U.S. Patent No, 6,254,874, hereinafter "Mekalanos")(Office Action item 9, page 7);
6. Claims 1, 3-5, 7-12 and 16-27 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by del Cardayre, *et al* (U.S. Patent No, 6,716,631, hereinafter "del Cardayre")(Office Action item 10, page 8).

1. **Objection to Claim 6.** Claim 6 is objected to as being dependent on a rejected base claim (Office Action item 5, page 3). Applicant believes that the rejection of the base claim should be withdrawn in view of the present amendments and remarks. Thus, Claim 6 is not presently redrafted in independent form and Applicant requests that this objection be held in abeyance until the standing of the independent claim from which it depends is resolved.

2. **Claims 1-12 are not indefinite.** The Examiner has rejected Claims 1-12 under 35 U.S.C. §112, second paragraph, alleging that the claims lack of clarity (Office Action item 6, page 3). In particular, the Examiner questions the clarity of Step b) in reciting " . . . an origin

of transfer from which conjugative transfer of the transferable plasmid *indicates* from the donor bacterium to at least one recipient bacterium." (*emphasis added).* Applicant notes that step b) of these claims recites "an origin of transfer from which conjugative transfer of the transferable plasmid *initiates* from the donor bacterium to at least one recipient bacterium." As described in the specification (*e.g.,* at page 6, lines 1-3), the conjugative process causes the transfer of the transmissible plasmid from a donor bacterium to a recipient bacterium. As recited in the claim, an origin of transfer is the site on the plasmid from which the transfer of the transmissible plasmid from the donor bacterium to the recipient bacterium is initiated. Applicant asserts that the language of the claim is clear to one of skill in the art. Claims 1-12 are thus not indefinite under §112, second paragraph, and Applicant respectfully requests that this rejection be removed.

Claim Amendments.

The claims are amended as indicated in the Listing of Claims. Support for the claims as amended is provided throughout the specification. For example, the use of a plasmid-based gene encoding a plasmid replication protein comprising a copy number control function is disclosed, *e.g.*, at page 7, lines 9-10. Reduction of the copy number control function of the plasmid-based gene by mutation is disclosed, *e.g.*, at page 8, lines 9-11, and page 17, lines 4-19. The use of a donor bacterium comprising a wild-type gene encoding a plasmid replication protein having a copy number control function is disclosed, *e.g.*, at page 7, line 29 to page 8, line 2. The use of a bifunctional plasmid replication protein comprising a plasmid replication activator function and a plasmid replication inhibitor function is disclosed, *e.g.*, at page 17, lines 6-8. Mutations in said bifunctional plasmid replication protein that cause runaway replication of a plasmid are disclosed, *e.g.*, at page 17, lines 10-15, and page 17 line 30, to page 18, line 3. Thus, the claims as amended are fully supported by the specification and do not comprise new matter.

3-6. The Claims Are Not Anticipated.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d. 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).* The Examiner alleges that each of the limitations in Claims 1, 3-4, 7-12 and 16-27 are anticipated by at least one of the references discussed in detail, below. Applicant respectfully disagrees. As discussed in detail below, none of the references recited

by the Examiner sets forth each and every element of the claims as amended, either expressly or inherently.

3. The Examiner has rejected Claims 1, 3-5 and 7-12 under 35 U.S.C. §102(b), alleging that these claims are anticipated by Mahan, *et al* (U.S. Patent No, 5,434,055, hereinafter "Mahan")(Office Action item 7, page 4). Applicant respectfully disagrees. Mahan does not teach each and every element of these claims, either expressly or inherently.

Claim 1 and dependent claims recite a recombinant donor bacterium harboring at least one transmissible plasmid. Both the donor bacterium and the plasmid are indicated to comprise specific features that are not taught or suggested by Mahan. In particular, the transmissible plasmid of these claims comprises features that include:

a) an origin of replication that is negatively controlled by a plasmid replication protein that has a copy number control function, such that, in the absence of the plasmid replication protein copy number control function, the transmissible plasmid undergoes runaway replication

b) a mutant gene encoding a plasmid replication protein comprising a copy number control function, wherein said mutant gene encoding said plasmid replication protein comprises a mutation that reduces the copy number control function of said plasmid replication protein;

c) an origin of transfer from which conjugative transfer of the transmissible plasmid initiates from the donor bacterium to at least one recipient bacterium;

d) at least one screenable marker gene.

These claims further specify that the donor bacterium comprises one or more transfer genes conferring upon the donor bacterium the ability to conjugatively transfer the transmissible plasmid to the recipient bacterium, and that the donor bacterium comprises a wild type gene encoding said plasmid replication protein comprising a copy number control function.

The Examiner asserts that Mahan teaches a recombinant bacterium harboring a plasmid, wherein the plasmid comprises a selectable marker, and further states that Mahan also teaches plasmids comprising an origin of transfer and an R6K origin of replication (Office Action, page 4). However, these features do *not* anticipate the presently claimed invention. Mahan does not teach the use of a plasmid replication repression system to suppress replication of the plasmid in the donor bacterium. In particular, Mahan does not

teach or suggest a recombinant bacterium harboring a transmissible plasmid, wherein the transmissible plasmid comprises an origin of replication that is negatively controlled by a plasmid replication protein comprising a copy number control function, wherein the plasmid also comprises a gene encoding a mutant plasmid replication protein having a reduced copy control function, and wherein the donor bacterium contains a gene encoding the wild type plasmid replication protein. Thus, Mahan fails to teach or suggest all elements of the Claims 1, 3-5 and 7-12, and does not anticipate these claims. Applicant therefore requests that this rejection be removed.

4. The Examiner has rejected Claims 1, 3-5, 7-12 and 16-27 under 35 U.S.C. §102(e), alleging that these claims are anticipated by Curtiss, III, *et al* (U.S. Patent No, 6,780,405, hereinafter "Curtiss")(Office Action item 8, page 5). Applicant respectfully disagrees. Curtiss does not teach each and every element of these claims as amended, either expressly or inherently.

The Examiner asserts that Curtiss teaches a number of elements, including a vector that includes an origin of replication repressable by a repressor; runaway vectors that can be transferred to or expressed in another cell; particular microorganisms; and killer genes, and asserts that the teachings of these features anticipate the claimed invention. Applicant disagrees with the characterizations of some of the elements taught by Curtiss, and with the Examiner's assertion that this list of disconnected elements anticipates the claimed invention.

Curtiss does not teach a donor bacterium comprising a transmissible plasmid configured such that the donor bacterium is configured to repress replication of the transmissible plasmid, and is also configured to conjugatively transfer that transmissible plasmid to a recipient pathogenic bacterium such that the transmissible plasmid undergoes runaway replication in the recipient bacterium.

Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the same or similar claims in the future, the claims are herein amended to recite a recombinant donor bacterium harboring at least one transmissible plasmid wherein the transmissible plasmid comprises:

a) an origin of replication that is negatively controlled by a plasmid replication protein that has a copy number control function, wherein in the absence of the plasmid replication protein copy number control function, the transmissible plasmid undergoes runaway replication

b) a mutant gene encoding a plasmid replication protein comprising a copy number control function, wherein said mutant gene encoding said plasmid replication protein comprises a mutation that reduces the copy number control function of said plasmid replication protein;

c) an origin of transfer from which conjugative transfer of the transmissible plasmid initiates from the donor bacterium to at least one recipient bacterium;

d) at least one screenable marker gene.

wherein the donor bacterium further comprises one or more transfer genes conferring upon the donor bacterium the ability to conjugatively transfer the transmissible plasmid to the recipient bacterium, and wherein the donor bacterium further comprises a wild type gene encoding said plasmid replication protein comprising a copy number control function, and further wherein the at least one recipient bacterium is a pathogenic bacterium that does not produce the plasmid replication protein comprising a copy number control function, thereby enabling the transmissible plasmid to undergo runaway replication in the recipient bacterium.

Curtiss does not teach or suggest a recombinant bacterium harboring a transmissible plasmid, wherein the transmissible plasmid comprises an origin of replication that is negatively controlled by a plasmid replication protein comprising a copy number control function, wherein the plasmid also comprises a gene encoding a mutant plasmid replication protein having a reduced copy control function, an origin of transfer, and a screenable marker, and wherein the donor bacterium contains transfer genes enabling conjugative transfer of the plasmid to a recipient bacterium, and a gene encoding the wild type plasmid replication protein. Thus, Curtiss fails to teach or suggest all elements of the Claims 1, 3-5, and 7-12 and does not anticipate these claims.

The Examiner has also rejected Claims 16-27 in view of Curtiss. Claims 16-27 relate to a recombinant donor bacterium harboring at least one transmissible plasmid, wherein the plasmid comprises a killer gene. The Examiner asserts that Curtiss teaches the use of a killer gene. In particular, the Examiner asserts that Curtiss teaches the use of the ColE1 gene as a killer gene (Office action page 6, pointing to Curtiss column 14). Applicant respectfully disagrees. Curtiss teaches the use of the ColE1 *replicon*, not the use of the gene encoding the colicin E1 toxin. The Examiner has provided no evidence that Curtiss teaches the use of a gene encoding a colicin toxin, or any other killer gene.

The recombinant donor bacterium and the transmissible plasmid of Claims 16-27 have additional specific elements that have specific relationships to each other. The transmissible plasmid of the claimed invention comprises: a) an origin of replication for synthesizing the plasmid in a bacterial cell; b) an origin of transfer from which conjugative transfer of the transmissible plasmid initiates from the donor bacterium to at least one recipient bacterium; c) at least one killer gene that, upon expression in a bacterial cell, produces a product that kills the cell; and d) at least one screenable marker gene. The donor bacterium is modified so as to be unaffected by the product of the killer gene. In addition to containing the transmissible plasmid, the donor bacterium further comprises one or more transfer genes conferring upon the donor bacterium the ability to conjugatively transfer the transmissible plasmid to a recipient bacterium.

Curtiss does not teach or suggest a recombinant bacterium comprising all of the elements recited above. For example, Curtiss does not teach a recombinant bacterium comprising a transmissible plasmid, wherein the transmissible plasmid comprises a killer gene, wherein the recombinant bacterium is modified so as to be unaffected by product of the killer gene.

For the reasons recited above, Applicant submits that Curtiss fails to teach or suggest all elements of the Claims 1, 3-5, 7-12, and 16-27, and thus does not anticipate these claims. Applicant therefore requests that this rejection be removed.

5. The Examiner has rejected Claims 1, 3-5, and 7-12 under 35 U.S.C. §102(e), alleging that these claims are anticipated by Mekalanos, *et al* (U.S. Patent No, 6,254,874, hereinafter "Mekalanos")(Office Action item 9, page 7). Applicant respectfully disagrees. Mekalanos does not teach each and every element of these claims, either expressly or inherently.

The Examiner asserts that Mekalanos teaches a recombinant bacterium harboring a suicide vector, wherein the suicide vector comprises a selectable marker, and further states that Mekalanos also teaches plasmids comprising an origin of transfer and an R6K origin of replication (Office Action, page 7). However, these features do *not* anticipate the presently claimed invention. Mekalanos does not teach the use of a plasmid replication repression system to suppress replication of the plasmid in the donor bacterium. In particular, Mekalanos does not teach or suggest a recombinant bacterium harboring a transmissible plasmid, wherein the transmissible plasmid comprises an origin of replication that is negatively controlled by a plasmid replication protein comprising a copy number control function, wherein the plasmid also comprises a gene encoding a mutant plasmid replication

protein having a reduced copy control function, and wherein the donor bacterium contains a gene encoding the wild type plasmid replication protein. Thus, Mekalanos fails to teach or suggest all elements of the Claims 1, 3-5 and 7-12, and does not anticipate these claims. Applicant therefore requests that this rejection be removed.

6. Claims 1, 3-5, 7-12 and 16-27 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by del Cardayre, *et al* (U.S. Patent No, 6,716,631, hereinafter "del Cardayre")(Office Action item 10, page 8)

As with the rejections in view of Mahan, Curtiss, and Mekalanos, the Examiner points to elements allegedly taught by del Cardayre and asserts that the disconnected list of elements anticipates the presently claimed invention. Applicant respectfully disagrees.

del Cardayre describes a number of methods of altering cells through genetic recombination. As aspects of such genetic recombination and selection, del Cardayre discloses a number of recombinant bacteria, plasmids, and plasmid elements. However, the disconnected list of elements recited by the Examiner neither includes all of the elements of the present claims, nor anticipates the presently claimed invention.

del Cardayre does not teach or suggest a recombinant bacterium harboring a transmissible plasmid, wherein the transmissible plasmid comprises an origin of replication that is negatively controlled by a plasmid replication protein comprising a copy number control function, wherein the plasmid also comprises a gene encoding a mutant plasmid replication protein having a reduced copy control function, an origin of transfer, and a screenable marker, and wherein the donor bacterium contains transfer genes enabling conjugative transfer of the plasmid and a gene encoding the wild type plasmid replication protein. Applicant notes that the "suicide vectors" of del Cardayre to which the Examiner points (Office action, page 8) are defined as lacking an origin of replication that functions in the recipient cells (see, *e.g.*, column 15 at line 33-34). This teaching is directly contrary to the teachings of the present invention regarding use of a transmissible plasmid that undergoes runaway replication in the recipient cell. Furthermore, del Cardayre does not teach a recombinant bacterium comprising a transmissible plasmid, wherein the transmissible plasmid comprises a killer gene, and wherein the recombinant bacterium is modified so as to be unaffected by product of the killer gene.

For the reasons recited above, Applicant submits that del Cardayre fails to teach or suggest all elements of the Claims 1, 3-5, 7-12, and 16-27, and thus does not anticipate these claims. Applicant therefore requests that this rejection be removed.

Applicant's claims are directed toward recombinant donor bacteria that are configured to kill other bacteria by transfer of a transmissible lethal plasmid. In some embodiments, the recipient cell is killed when the plasmid undergoes runaway replication, which is defined in the specification as plasmid replication that is completely unchecked due to the loss of copy control mechanisms (see, *e.g.*, pages 7, lines 6-8). In other embodiments, the recipient cell is killed by the product from a "killer gene" on the plasmid (see, *e.g.*, page 11, line 15 to page 13, line 6). In both instances, the donor bacteria are specially configured so as to avoid the killing effect of the plasmid. In the case of runaway replication, the bacterium comprises a functional copy of a replication protein that controls plasmid copy number, while for use with the plasmids having killer genes, the bacterium is modified so as to be unaffected by product of the killer gene. In addition, Applicant has enabled these embodiments. In a declaration filed with the last response, Applicant provided numerous examples of "real world" data showing the efficacy of killing recipient bacteria on a variety of surfaces by conjugative transfer to them of the killer plasmids and killer genes of the present invention.

The recombinant bacteria and plasmids of the present invention comprise a number of genes and control elements that are widely used by those of skill in the art. As such, these terms are easily found in the prior art when used as search terms. However, in the presently claimed invention, the genes and control elements are used in particular novel combinations that are arranged to achieve particular functionality, *i.e.*, the ability to kill recipient cells by the transfer of a plasmid, wherein such killing may be achieved in different ways (e.g. runaway plasmid replication or expression of a lethal gene), as described above. As discussed in detail above, none of the prior art cited by the Examiner disclosed or suggested each and every one of the elements of the present claims in the particular novel combinations recited in the claims. Thus, the claims are not anticipated and each of the rejections under 35 U.S.C. § 102 should be removed.

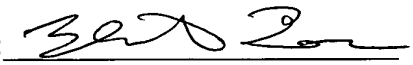
CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and should be removed, and that Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at 414-277-5633.

No extension of time is believed to be necessary and no fee is believed to be due in connection with this response. However, if any extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055. No other fee is believed to be due in connection with this response. However, if any fee is due in this or any subsequent response, please charge the fee to the same Deposit Account No. 17-0055.

Respectfully submitted,
Marcin S. Filutowicz

November 22, 2004

By: 

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